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82. (New) The method of claim 81, wherein said differentiated proliferating cell has been expanded in culture.

REMARKS

This amendment is responsive to the Office Action dated August 4, 1999. Entry of the foregoing and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 CFR §1.112, are respectfully requested.

At the outset, applicants note that several amendments to the claims were proposed above. In particular, claim 11 was amended to include germ cells as one type of donor cell that may be used in the method of claim 1. Support for this amendment is found on page 23, line 15 of the specification. Claims 18, 19, 21, 22, 26, 27, 34, 35, 49, 51, 53, 56, 58, 60, and 76 have been amended to distinguish the claimed embryos, fetuses, offspring, CICM cell lines, differentiated cells derived therefrom, and transgenic and chimeric derivatives of the same from other such entities known in the art, by noting that the products of the present invention have a genotype identical to a prior-existing differentiated cell, fetus or mammal (with the exception of genetic alterations in transgenic animals), wherein said prior-existing cell, fetus or mammal was not created by nuclear transfer techniques. Embryos, fetuses, and animals not created according to the present methods, i.e., created by normal breeding techniques, would never have such a characteristic, as they would have a genotype that is derived from both parents. The limitation now recited in the claims is an inherent feature of the embryos, fetuses and animals created by the present invention, and therefore finds support in the application as a whole. No new matter has been added.

The claims have also been amended to comply with some of the Examiner's suggestions in the Office Action. For instance, claims 47, 48, 50, 52, 54, 55, 57, and 59 have been amended to reword these claims as suggested following the rejections set forth under 35 U.S.C. §112, second paragraph. Claim 78 has also been amended as suggested to correct dependency. No new matter has been added.

New claims 79-82 have also been added in order to stress that the differentiated cells to be used in the invention are proliferating cells, and that such proliferating cells may be expanded in culture prior to nuclear transfer (for instance in the case where genetic alterations are desirable), or used directly without expansion (as in the case where an animal with desirable genetic traits is cloned). Support for such claims may be found at the very least on page 10, lines 9-15, and page 47, lines 4-6. No new matter has been added.

Turning now to the Office Action, claims 1-17, 24, 25, 61 and 63 were rejected for alleged obvious-type double patenting. Applicants respectfully request that this rejection be held in abeyance until the indication of allowable subject matter, as the content of the claims may change by amendment during prosecution. If at the time an allowance is agreed upon the Examiner still believes that the claims are obvious over application Serial No. 08/781,752, applicants will submit a terminal disclaimer.

Next, claims 1-17, 24, 25, 29, 30, 32, 34, 46-48, 50, 52, 54, 55, 57, 59, 61-63 and 78 were rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly fails to describe the subject matter of the claims in such a way as to enable those of skill in the art to make and or/use the invention. Essentially, it is the Examiner's opinion that cloning pigs, or methods of making pharmaceutically active proteins using pigs, or methods of making chimeric pigs, would not have a reasonable expectation of success at the time the application

was filed in view of the disclosure and the nature of the art. Applicants respectfully traverse the rejection.

Firstly, Applicants respectfully note that the rejection is contradictory to the Examiner's previous allowance of application Serial No. 08/781,752, which, as the Examiner herself indicates in the obvious type double patenting rejection set forth in the Office Action, contains a claim specifically directed to cloning pigs. Although applicants understand that a genus claim will sometimes be patentable where a species claim would not be, where the specific species is explicitly recited in an allowed dependent claim, it would seem that there exists a presumption of patentability for such species that must be respected. This would seem to be particularly true regarding the requirements of 35 U.S.C. §112, where the application at issue is a continuation-in-part of the patented disclosure.

Notwithstanding the presumption of patentability for methods of cloning pigs, applicants will respectfully review the relevant arguments as presented in the parent application. Enablement of the disclosed method was discussed in great detail in a previous interview with the Examiner. The details of what was discussed at that interview, as well as a §132 Declaration by one of the inventors of the instant application, were entered into the parent file preceding allowance of the parent application. In such documentation, it was explained that the subject invention comprises a pioneering discovery, i.e., that somatic cells or cells committed to a somatic cell lineage may be used as nuclear transfer donors for cloning desired non-human mammals by nuclear transfer techniques. It was indicated that this was a surprising discovery as it was contravened by previous accepted dogma in the art. Essentially, prior to the present invention, it was thought that once a cell becomes differentiated that it loses its ability to be a suitable donor cell during nuclear transfer. More

specifically, as explained in Dr. Robl's Declaration, it was widely thought by researchers working in the area of cloning prior to the present invention that, once a cell becomes committed to a particular somatic cell lineage, its nucleus irreversibly loses its ability to become "reprogrammed", i.e., to support full-term development when used as a nuclear donor for nuclear transfer. Applicants would be happy to submit a copy of the Declaration previously submitted in the parent application if this would be helpful.

It was further argued, and also substantiated by supporting documentation, that the subject cloning method is generically applicable to non-human mammals, and that the efficacy of the subject cloning protocol should not be limited to any particular species. To the contrary, Applicants have made a generic discovery, namely that non-human mammals may be successfully cloned by nuclear transfer using as the nuclear transfer donor a somatic cell or nucleus derived therefrom which is capable of division.

The Office Action also questions the intended use of the chimeric or transgenic mammals of the present invention. In response, Applicants respectfully submit that, because the nucleus of an adult differentiated cell could be used to make such cell lines, and differentiated cells maybe readily maintained in culture and easily modified genetically, cloned pigs resulting from the claimed methods could be used as a source of tissues for xenotransplantation. Indeed, as stated in the February 1, 2000 edition of the Financial Times Ltd, "officials have said that humans could start to receive transplanted organs from pigs within the next five to seven years," and that "some companies are cloning pigs from a nucleus with implanted genes to make certain organs and processes more compatible for use in humans."

The Office Action also questions, however, whether any given transgene would be expressed sufficiently so as to immunize a transplanted organ from rejection (Office Action, page 5). Applicants respectfully point out that the methods of the present invention make the use of heterologous genes as transgenes more predictable and reliable, since a nuclear donor may be selected which is transfected beforehand, and has already been shown to demonstrate sufficient transgene expression.

Thus, the concern discussed in the Office Action that a transgene would need to be expressed "sufficiently" does not raise an issue with regard to unpredictability because the methods of the present invention are a simplification over the methods of the prior art. Indeed, a differentiated cell having a genotype of interest may be transfected with a gene of interest before nuclear transfer, and selection of a cell containing a nucleus from which the transfected gene is sufficiently expressed may be accomplished without using cytokines, and without worrying about differentiation of the cells. The method of the present invention therefore removes the unpredictability element from the expression of transgenes in transgenic animals, and of course such genes could be chosen for the purpose of preventing or deterring the rejection of transplants.

The Office Action also states that it is not useful how animals that do not express a transgene would be useful, and that the specification fails to disclose other clear uses. With all due respect, applicants fail to comprehend why other uses of cloned animals are "not apparent" given the extreme competition in the art to produce such animals. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent *coupled with information known in the art.*" *U.S. v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1223 (Fed. Cir. 1988) (With emphasis.) Because the "use" prong of

35 U.S.C. §112, first paragraph, is also evaluated in consideration of what is known in the art, one need only look at any of the multitude of references currently available discussing the potential uses of cloned animals.

For example, as remarked by President Clinton in a statement he made on cloning (March 4, 1997): "The recent breakthrough in animal cloning is one that could yield enormous benefits, enabling us to reproduce the most productive strains of crop and livestock, holding out the promise of revolutionary new medical treatments and cures, [and] helping to unlock the greatest secrets of the genetic code." In fact, either transgenic or non-transgenic pigs expressing desirable traits would be benefitted by cloning in that prize animals could be propagated without jeopardizing the genotype through the process of breeding. Indeed, just because one has already developed a germline stable transgenic animal does not mean that the propagation of such an animal would not also benefit by the cloning techniques disclosed herein; the expression of other undesirable genes which might be introduced through the process of breeding is just as much a threat to animals that are already transgenic, as it is to those that are not, and to those which are made simultaneously with the cloning process.

Thus, given the previous allowance of a cloning method for pigs based on the disclosure of the parent application, and given the extensive arguments regarding the utility and operability of the invention in the parent application and again above, reconsideration and withdrawal of the rejection is respectfully requested.

Next, claims 29, 47, 48, 50, 52, 54, 55, 57, 59, and 78 were rejected under 35 U.S.C. §112, second paragraph for issues relating to claim format and dependency. These issues, raised in the Office Action on page 9, have been corrected by way of amendment above.

Thus, the rejections are now moot. Reconsideration and withdrawal of the rejection is respectfully requested.

Finally, claims 18-23, 26-28, 31, 35, 49, 51, 53, 56, 58, 60, 64, 65 and 71-76 were rejected under 35 U.S.C. §102 in view of various references concerning pig embryos, fetuses, offspring, and transgenic and chimeric derivatives, for essentially the same argument for each rejected claim, namely, the cloned, transgenic and chimeric pigs, pig embryos, and pig fetuses claimed in the instant invention are allegedly not patentably distinct over pigs in general known in the art, because they are allegedly the same except that they were made by a different process. Claim 33 was rejected for a similar rationale under 35 U.S.C. §103(a) in view of Strojek, which allegedly teach that ICM cells can be transformed to provide a method for producing transgenic livestock.

While not necessarily agreeing with the rejection, applicants respectfully note that the claims have been amended to differentiate the pigs, pig embryos and pig fetuses of the present invention from those of the prior art and not generated by cloning, by clarifying that the animals of the present invention have a unique genotype that would not be found in animals, embryos and fetuses that were not generated by cloning. Namely, because the claimed embryos, fetuses, offspring, progeny and cell line are made from an NT unit which is in turn made using the nucleus from a differentiated cell, the claimed embryos, fetuses, offspring, progeny and cell line of the present invention may be distinguished from similar products in the prior art in that they have the identical genotype as a differentiated cell, fetus or mammal of the same species in existence prior to nuclear transplantation, wherein such prior existing cell, fetus or mammal was not formed using nuclear transfer techniques. The probability of

this happening purely by chance with any other embryo, fetus, offspring or progeny is virtually zero.

Accordingly, it appears that the rejections under 35 U.S.C. §102 and §103(a) are moot in view of the amendments made above. Reconsideration and withdrawal is respectfully requested.

Applicants believe that the above constitutes a complete response to the Office Action. Accordingly, a Notice of Allowance is next in order. If the Examiner would like to discuss the amendment or the application in general, she is respectfully requested to telephone the undersigned.

Respectfully submitted,

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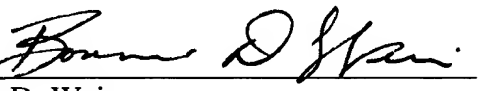
By: 

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